

REMARKS

Amendments to the specification:

The specification has been amended to correct typographical and/or editorial errors where "Example 28" was typed instead of "Example 27."

Applicants have also amended the specification correct typographical and/or editorial errors regarding ATCC Deposit Numbers and clone IDs. The correct relationship between ATCC Deposit Numbers and the molecules encoded by the cDNA clone therein is shown in the table below.

Applicants submit herewith a copy of the ATCC deposit receipt (dated October 7, 1997) (Exhibit A). The ATCC deposit receipt links each ATCC Deposit Number with a "DNA Plasmid" number. Each DNA sequence in the HGS electronic database is assigned an unchangeable DNA Plasmid number as a unique identifier. Applicants submit herewith a separate printout from the HGS electronic database to link a particular cDNA clone in the present application to the DNA Plasmid number that appears on the ATCC deposit receipt (Exhibits B, C, and D). Applicants submit herewith a copy of a declaration by inventor Jian Ni (filed in Parent Application 09/176,200 on May 19, 2000, to which the instant application claims priority) affirming the relationship between cDNA clones HHEAC71, HT5EA78, and HCFAZ22 and DNA Plasmid numbers 1724062, 2136388, and 1129852, respectively. Thus, the information in the following table may be used to summarize the link between the ATCC Deposit Number recited on the deposit receipt, the molecule encoded by the cDNA clone deposited therein, the "DNA Plasmid" number recited on the ATCC deposit receipt, a printout from the HGS electronic database, and the specification of the captioned application.

ATCC Deposit No.	Molecule Encoded	DNA Plasmid No.	HGS Electronic Identifier	Reference in Captioned Specification
209341	TR11	1724062	HHEAC71 (Exhibit B)	At page 8, lines 18-26
209342	TR11SV2	2136388	HT5EA78 (Exhibit D)	At page 8, lines 18-26
209343	TR11SV1	1129852	HCFAZ22 (Exhibit C)	At page 8, lines 18-26

No new matter has been added by way of amendment. Applicants respectfully request that the amendments to the specification be entered.

Status of the claims:

Claims 47 and 48 drawn to non-elected inventions have been cancelled without prejudice. Applicants reserve the right to pursue the subject matter of the cancelled claims in related applications. Claims 19-46 are currently pending.

Amendments to the claims:

Claims 19 has been amended to delete originally presented subparts (d) through (i); Claim 33 has been amended to delete originally presented subparts (c) through (i); and new subparts 19(d) and 33(c), respectively, drawn to polypeptide fragments of either the polypeptide of SEQ ID NO:2 or encoded by the cDNA in ATCC deposit 209341, have been added. Support for newly present subparts (d) and (c) of claims 19 and 33, respectively, may be found throughout the specification as filed, such as at page 76, lines 3-18 (as amended); page 43, lines 14-30; pages 46-50 and 58 to 61. Claim 33 has also been amended to recite domains or fragments of the polypeptide encoded by the ATCC deposit number 209341, rather than reciting specific amino acid residues of SEQ ID NO:2. Support for this amendment, may be found, for example, in the paragraph spanning pages 21-22 (as amended). The claims as amended are completely supported by the specification as filed. No new matter has been added by way of amendment. Applicants respectfully request that the amendments to the claims be entered.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 19-46 are rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner contends that “claims 19-46 are indefinite because it is not clear how claims 19 and 33 (each independent claims from which 20-32 and 34-46, respectively, depend) differ in scope.” (See, Paper No. 11, paragraph 6).

Applicants respectfully disagree. The meaning of claims 19 and 33 (both before and after amendments made herein) is definite. M.P.E.P §2173.04 states that Breadth of a claim is not to be equated with indefiniteness.

In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 19-46 are also rejected under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner states:

The basis for this rejection is two-fold. First, newly added claims 19-46 appear to introduce new matter into the specification as originally filed because newly added claims 19-46 are drawn to methods using fragments of SEQ ID NO:2 that are not described in the specification. Thus, it appears that claims 19-46 are drawn to methods that were not contemplated at the time of filing. Secondly, claims 19-46 are drawn to methods using a genus of polypeptide molecules, the species of which vary widely in structure, and for which the structure of SEQ ID NO:2 does not appear to be a representative amino acid sequence.

Applicants respectfully disagree and traverse this rejection. The Examiner alleges that there is no literal support for subsections (c) through (i) of claims 19 and 33. Regarding subsection (c), literal support for this claim is provided in Example 27. Under the heading "Recombinant protein production and purification," on page 220, there is disclosed the use of a TR11-Fc-fusion protein comprising amino acids 26 to 139 (which corresponds to amino acids 1 to 114 of SEQ ID NO:2). Applicants note that this text was not referenced as supporting text for the new claims their Provisional Election and Amendment filed June 4, 2001, and apologize for the omission.

Regarding support for subsections (d) through (i), Applicants disagree that no literal support can be found in the specification for the polypeptide fragments recited therein and refer the Examiner to disclosure on pages 46-50 and 58 to 61, particularly lines 16-21 of page 50 and 16- 19 of page 61. Nonetheless, Applicants have amended claims 19 and 33, deleting subparts (d) through (i) of claim 19 and subparts (c) through

(i) of claim 33 as originally presented and replacing them with new subparts (d) and (c), respectively.

The Examiner is also concerned with the use of open language with regard to the polypeptide species recited in claims 19 and 33, because it is her contention that the structures of the broadly claimed polypeptides is not “fully recited in the claims and are not taught in the specification.” (See Paper No. 11, page 5, paragraph B). As cited above, the Examiner holds that SEQ ID NO:2 is not a representative amino acid sequence for the claimed genus of polypeptides.

Applicants respectfully disagree and traverse.

Example 27 clearly defines a TR11Fc fusion protein comprising amino acids 1-114 of SEQ ID NO:2 (or amino acids 26-139 of Figure 1) that binds endokine-alpha. Thus, a polypeptide comprising at least amino acids 1-114 of SEQ ID NO:2 (e.g., the polypeptides of subparts (a) through (c) of claims 19 and subpart (a) and (b) of claim 33) would also be expected to bind endokine-alpha. Likewise, it is well within the abilities of one of ordinary skill in the relevant arts to determine if a polypeptide fragment of the TR11 polypeptide (subpart (d) of claim 19 and subpart (c) of claim 33 as amended) binds endokine-alpha using standard methods of recombinant DNA technology and protein expression coupled with, for example the ligand binding assay described in Example 27 (see discussion of second 35 U.S.C. §112, first paragraph below). All of the claimed polypeptides have a common structural feature – the endokine-alpha binding moiety of TR11. Thus, contrary to the Examiner’s assertion. SEQ ID NO:2 is the relevant representative amino acid sequence of the genus of claimed polypeptides.

To assert that SEQ ID NO:2 is not a representative amino acid sequence is to suggest that there is a large portion of polypeptides within the claimed genus of TR11 polypeptides that inhibit binding of endokine-alpha to endogenous endokine-alpha receptors not via the TR11 moiety of the polypeptide, but through the non-TR11 moiety (if any) of the polypeptide. Given that each of subparts (a) through (d) of claims 19 and 33 (as amended) contain the endokine-alpha binding moiety of TR11, this as an improper construction of the claim in light of the specification.

In light of the amendments to claims 19 and 33 and above remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, as set forth on pages 3-5 of Paper No. 11, be withdrawn.

Claims 19-46 are also rejected under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. Specifically the Examiner states that

“[b]ecause of the breadth of the claims with respect to the widely varying amino acid structures and because of the unpredictability of protein chemistry with respect to the function of proteins, the specification, by only teaching one example and failing to teach a region of SEQ ID NO:2 that is critical for binding with soluble endokine-alpha, one of skill in the art would have to engage in undue experimentation to make the inventions as claimed.” (Paper No. 11, page 7)

Under this second 35 U.S.C. § 112, first paragraph rejection, the Examiner reiterates the contention that the structures of the TR11 polypeptides are not completely recited in the claims. Applicants have responded to this point above, and will not belabor the issue here. As regards the “unpredictability of protein chemistry,” the Examiner cites examples where single amino acid changes have drastically alter the function of a polypeptide. Applicants note that in addition to such examples being the exception rather than the rule, Applicants’ claims are directed to polypeptides comprising endokine-alpha binding fragments of SEQ ID NO:2. The Examiner has in no way explained how the present claims raise the issue of “widely varying amino acid structures.”

The Examiner acknowledges that there is data in the specification (Example 27) showing that a polypeptide having the amino acid sequence of SEQ ID NO:2 binds to soluble endokine-alpha, and that specification is enabling for the use of the polypeptide of SEQ ID NO:2 to inhibit the binding of endokine-alpha to endokine-alpha receptors. Applicants note that Example 27 shows both that 1) a TR11 flag fagged protein comprising amino acids 1-209 of SEQ ID NO:2 (or 26-234 of Figure 1 which is not quite the full length protein as assumed by the Examiner, but rather is the full length protein minus the signal sequence), when expressed in a HEK293 cells triggers NF-kappaB activation after exposure to soluble endokine-alpha; and 2) that an Fc Fusion protein comprising amino acids 1-114 of SEQ ID NO:2 (26-139 of Figure 1) binds soluble endokine-alpha. Thus, Applicants have provided all that is necessary for one of skill in the art to carry out the claimed methods *without undue experimentation*. It is not

necessary to determine the critical endokine-alpha binding region in order to practice the claimed invention.

Even assuming, for the sake of argument, that carrying out the claimed methods required determining the precise boundaries of the endokine-alpha binding region, one of skill in the art at the time of the filing this application would certainly have been able to define the critical endokine alpha binding region, without undue experimentation. At the time of the filing of this application, recombinant DNA techniques and protein expression protocols were well within the abilities of one skilled in the art. Applicants submit herewith as Exhibits E, F, and G, respectively, three references illustrating assays known in the art well before the priority date of the instant application that clearly demonstrate that detection of functional peptide fragments by deletion mapping was entirely routine (Munro and Pelham, *EMBO J.* 3:3087-3093 (1984); Pollard et al., *EMBO J.* 11:585-591 (1992); Sugiyama et al., *PNAS* 88:9603-9607 (1991)). In fact, these references were publicly available in 1984, 1991, and 1992, and are merely representative examples of the state of the art. Thus it is entirely within the abilities of one of skill in the relevant art, at the time the application was filed, to construct TR11 deletion mutants and to test, without undue experimentation, their ability to bind endokine-alpha using assays well known in the art, such as the endokine-alpha binding assay described in Example 27.

The Examiner further alleges that the "specification fails to teach how to use the claimed methods for any specific purpose;" that "the specification fails to teach the identity of endogenous endokine-alpha receptors;" and that there is not, either in the art or in the specification, a correlation between endokine alpha and a disease state. Applicants respectfully disagree.

The specification teaches that endokine-alpha is described in International Publication No. WO 98/07880, published February 26, 1998 (See, for example, the last line of page 218 through line 2 of the page 219). WO 98/07880 is cited as reference C1 on the revised form SB-08 submitted herewith; a copy of this reference is also submitted herewith. WO 98/07880 teaches that endokine-alpha is about 30% similar and 22% identical to Human Tumor Necrosis Factor-alpha (WO 98/07880, page 10, lines 1-3). Based on this homology it is asserted that human endokine-alpha encodes a cytokine with biological effects and activities similar to TNF. (*Id.* at page 5, lines 15-17). WO 98/07880 further teaches that endokine-alpha plays a role in, for example, pro-inflammatory actions (*Id.* at pages 2-4). Thus, inhibiting endokine alpha binding to

endogenous endokine alpha receptors may be used to inhibit inflammatory reactions as is asserted in the instant specification, for example, at page 147, lines 9-18 combined with the disclosure at page 144, line 21 through page 145, line 4. Furthermore, Applicants' experimental work described in Example 27 has confirmed this assertion of utility, by showing that endokine alpha interaction with TR11 expressed on the surface of HEK293 EBNA cells activates the NF-kappa B transcription factor. Applicants demonstration that endokine-alpha binds TR11, is indicative of the fact that TR11 is an endogenous endokine-alpha receptor. NF-kappa B is known in the art to be to be a transcription factor involved in the pro-inflammatory response. (see, e.g., Renard and Raes, *Cell Biol. Toxicol.* 15:341-4 (1999) and Lentsch and Ward *Arch. Immunol. Ther. Exp. (Warsz)* 48:59-63 (2000) (Exhibits H and I, respectively.)

In conclusion, Applicants remind the Examiner that utility can exist for therapeutic inventions "despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition." M.P.E.P, 8th edition, 2107 (III) at 2100-35. Applicants have provided a method of inhibiting the pharmacological activity of endokine-alpha (activation of NF-kappa B), which under case law constitutes a showing of practical utility. *Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980). Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under § 101.

Rejections Under 35 U.S.C. §§102 and 103

Claims , 19-21, 26, 27, 33-35, 40 and 41 are were rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent 6,111,090 to Gorman et al (Gorman [a]).

Claims 19-21, 26, 27, 33-35, 40 and 41 are rejected under 35 U.S.C. §102(b) as being anticipated by International patent publication WO98/06842 (Gorman [b]).

Claims 19, 21-24, 33, 35-38 are rejected under 35 U.S.C. §103(a) as being unpatentable over either Gorman [a] or Gorman [b] in view of U.S. patent 5,116,964 to Capon et al.

Claims 19, 21, 25, 33, 35, and 39 are rejected under 35 U.S.C. §103(a) as being unpatentable over either Gorman [a] or Gorman [b] in view of U.S. patent 5,116,944 to Sivam et al.

Claims 19,28-31, 33 and 42-45 are rejected under 35 U.S.C. §103(a) as being unpatentable over either Gorman [a] or Gorman [b].

This rejection is obviated by the fact that neither the Gorman [a] or Gorman [b] references teach that TR11 binds endokine-alpha, or that TR11 can be used to inhibit the binding of TR11 to endogenous endokine-alpha receptors. In order for a reference to be anticipating under 35 U.S.C. §102(a), (b) or (e), it must teach every element of a claim. (See, M.P.E.P. §2131). As the Gorman references fail to teach an essential element of the claims of the instant application, they cannot be used to support an anticipation rejection under either 35 U.S.C. §102(b) or (e). Likewise, in order for a set of references to render a claim obvious, the combination of references must also teach every element of the claim. (See, M.P.E.P. §2142).

There is one exception to the rule that a reference to must teach every element of a claim to be anticipating under 35 U.S.C. §102(a), (b) or (e) which lies in the fact that a reference may *inherently* disclose an element of a claim. Two distinct showings are required to establish inherent anticipation: first, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the prior art reference; and second, such inherent characteristic would have to have been recognized by a person of ordinary skill in the art at the time of the invention. *Glaxo Inc. v. Novopharm Ltd.*, *supra*, 52 F.3d at 1047, 34 USPQ2d at 1567; *Continental Can Co. USA Inc. v. Monsanto Co.*, *supra*, 948 F2d at 1268, 20 USPQ2d at 1749; *Mickowski v. Visi-Trak Corp.*, 36 F. Supp.2d 171 (SDNY 1999). As, it has not been shown that binding to endokine-alpha will necessarily result from administering a TR11 polypeptide to a mammal or that a person of ordinary skill in the art would have recognized that TR11 binds endokine-alpha at the time of the invention, a case for inherent anticipation cannot be made over the cited Gorman references.

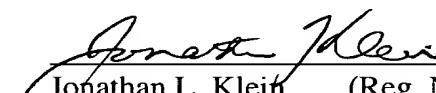
Since, none of the cited references teach that TR11 binds endokine-alpha, or that TR11 can be used to inhibit the binding of TR11 to endogenous endokine-alpha receptors, either inherently or expressly, they cannot support an obviousness rejection under 35 U.S.C. §103(a). Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §§102(b), 102(e), and 103(a), be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the present application. The application is believed to be in condition for allowance. Early notice to that effect is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below. If a fee is required in connection with this paper, please charge Deposit Account No. 08-3425 for the appropriate amount.

Respectfully submitted

Dated: January 23, 2002



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Attachment
#14

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ni et al.

Application No.: 09/512,363

Art Unit: 1642

Filed: February 23, 2000

Examiner: Holleran, A

For: Human Tumor Necrosis Factor
Receptor-Like Proteins TR11,
TR11SV1 and TR11SV2

Atty Docket No.: PF396P1

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendments are shown in boldfaced text with insertions indicated by underlining and deletions indicated by strikeout.

In the Specification:

The paragraph spanning lines 10-20 of page 4 has been replaced with the following amended paragraph:

The present invention provides isolated nucleic acid molecules comprising or alternatively consisting of, polynucleotides encoding TR11, TR11SV1, and TR11SV2 receptors having the amino acid sequences shown in Figures 1A and 1B (SEQ ID NO:2), 2A and 2B (SEQ ID NO:4), and 3A and 3B (SEQ ID NO:6), respectively, or the amino acid sequences encoded by the cDNA clones encoding the TR11, TR11SV1, and TR11SV2 receptors, respectively, deposited as ATCC Deposit Numbers 209341, **209342**, ~~and 209343~~ 209343 and 209342, respectively, on October 7, 1997. The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells and for using them for production of TR11, TR11SV1, and TR11SV2 polypeptides or peptides by recombinant techniques.

Please replace the paragraph spanning lines 7-25 of page 10 has been replaced with the following amended paragraph:

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding TR11, TR11SV1, and TR11SV2 polypeptides (Figures 1A and 1B, 2A and 2B, and 3A and 3B (SEQ ID NO:2, SEQ ID NO:4, and SEQ ID NO:6, respectively), the amino acid sequences of which were determined by sequencing cloned cDNAs. The TR11, TR11SV1, and TR11SV2 proteins shown in Figures 1A and 1B, 2A and 2B, and 3A and 3B, respectively, share sequence homology with the human mGITR receptor-like protein (Figure 2 (SEQ ID NO:7)). On October 7, 1997, deposits of plasmid DNAs encoding TR11, TR11SV1, and TR11SV2 were made at the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209, and given accession numbers 209341, ~~209342, and 209343~~ 209343 and 209342, respectively. The nucleotide sequences shown in Figures 1A and 1B, 2A and 2B, and 3A and 3B (SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5, respectively) were obtained by sequencing cDNA clones (Clone ID HHEAC71, ~~HTSEA78 and HCFAZ22~~ HCFAZ22 and HTSEA78, respectively) containing the same amino acid coding sequences as the clones in ATCC Accession Nos. 209341, ~~, 209342, and 209343~~ 209343 and 209342, respectively. The deposited clone encoding TR11 is contained in the pCMV Sport3.0 plasmid (Life Technologies, Rockville, MD). The deposited clone encoding TR11SV1 is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The deposited clone encoding TR11SV2 is contained in the pSport1 plasmid (Life Technologies, Rockville, MD).

The paragraph bridging pages 12-13 has been replaced with the following amended paragraph:

As indicated, the present invention also provides mature forms of the TR11 and TR11SV2 receptors of the present invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species on

the protein. Further, it has long been known that the cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide. Therefore, the present invention provides nucleotide sequences encoding mature TR11 and TR11SV2 polypeptides having the amino acid sequences encoded by the cDNA clones contained in ATCC Deposit Numbers 209341 and 209343 209342 and as shown in Figures 1A and 1B and 3A and 3B, respectively (SEQ ID NO:2 and SEQ ID NO:6, respectively). By the mature TR11 and TR11SV2 polypeptides having the amino acid sequences encoded by "the cDNA clones contained in ATCC Deposit Numbers 209341 and 209343 209342" is meant the mature form(s) of the TR11 and TR11SV2 receptors produced by expression in a mammalian cell (e.g., COS cells, as described below) of the complete open reading frame encoded by the human DNA sequence of the deposited clones.

The paragraph spanning lines 6-16 of page 14 has been replaced with the following amended paragraph:

As one of ordinary skill would appreciate, however, due to the possibilities of sequencing errors, as well as the variability of cleavage sites for leaders in different known proteins, the TR11, TR11SV1, and TR11SV2 receptor polypeptides encoded by the cDNAs of ATCC Deposit Numbers 209341, 209342, and 209343 209343 and 209342, respectively, comprise about 241 amino acids (but may be anywhere in the range of 224 to 251 amino acids), about 241 amino acids (but may be anywhere in the range of 231 to 251 amino acids), and about 240 amino acids (but may be anywhere in the range of 230 to 250 amino acids). Further, the predicted leader sequences of these proteins are about 25, 0, and 19 amino acids, but the actual leaders may be anywhere in the range of about 15 to about 35, about 20 to about 40, and about 9 to about 29 amino acids, respectively.

The paragraph bridging pages 15-16 has been replaced with the following amended paragraph:

In another aspect, the invention provides isolated nucleic acid molecules encoding the TR11, TR11SV1, and TR11SV2 polypeptides having the amino acid sequence encoded by the cDNA clones contained in the plasmids deposited as ATCC Deposit Nos. 209341, 209342, and 209343 209343 and 209342, respectively, on October 7, 1997. In a

further embodiment, these nucleic acid molecules will encode a mature polypeptide or the full-length polypeptide lacking the N-terminal methionine. The invention further provides isolated nucleic acid molecules having the nucleotide sequences shown in Figures 1A and 1B (SEQ ID NO:1), 2A and 2B (SEQ ID NO:3), and 3A and 3B (SEQ ID NO:5), the nucleotide sequences of the cDNAs contained in the above-described deposited clones; or nucleic acid molecules having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, are useful as probes for gene mapping, by *in situ* hybridization with chromosomes, and for detecting expression of the TR11, TR11SV1, and TR11SV2 receptor genes of the present invention in human tissue, for instance, by Northern blot analysis.

The paragraph bridging pages 21-22 has been replaced with the following amended paragraph:

Further embodiments of the invention include isolated nucleic acid molecules comprising a polynucleotide having a nucleotide sequence at least 80%, 85% or 90% identical, and more preferably at least 95%, 96%, 97%, 98% or 99% identical to: (a) a nucleotide sequence encoding the TR11 polypeptide having the complete amino acid sequence shown in Figures 1A and 1B (amino acid residues -25 to 209 in SEQ ID NO:2); (b) a nucleotide sequence encoding the TR11SV1 polypeptide having the complete amino acid sequence shown in Figures 2A and 2B (amino acid residues 1 to 241 in SEQ ID NO:4); (c) a nucleotide sequence encoding the TR11SV2 polypeptide having the complete amino acid sequence shown in Figures 3A and 3B (amino acid residues -19 to 221 in SEQ ID NO:6); (d) a nucleotide encoding the complete amino sequence shown in Figures 1A and 1B but lacking the N-terminal methionine (i.e., amino acids -24 to 209 in SEQ ID NO:2); (e) a nucleotide encoding the complete amino sequence shown in Figures 2A and 2B but lacking the N-terminal methionine (i.e., amino acids 2 to 241 in SEQ ID NO:4); (f) a nucleotide encoding the complete amino sequence shown in Figures 3A and 3B but lacking the N-terminal methionine (i.e., amino acids -18 to 221 in SEQ ID NO:6); (g) a nucleotide sequence encoding the predicted mature TR11 receptor comprising the amino acid sequence at positions from 26 to 234 in Figures 1A and 1B (amino acid residues 1 to 209 in SEQ ID NO:2); (h) a nucleotide sequence encoding the predicted mature TR11SV1 receptor comprising the amino acid sequence at positions from 1 to 241 in Figures 2A and 2B (amino acid residues 1 to 241 in SEQ ID NO:4); (i) a nucleotide

sequence encoding the predicted mature TR11SV2 receptor comprising the amino acid sequence at positions from 20 to 240 in Figures 3A and 3B (amino acid residues 1 to 221 in SEQ ID NO:6); (j) a nucleotide sequence encoding the TR11 polypeptide having the complete amino acid sequence including the leader encoded by the cDNA clone contained in ATCC Deposit Number 209341; (k) a nucleotide sequence encoding the TR11SV1 polypeptide having the complete amino acid sequence including the leader encoded by the cDNA clone contained in ATCC Deposit Number 209342 209343; (l) a nucleotide sequence encoding the TR11SV2 polypeptide having the complete amino acid sequence including the leader encoded by the cDNA clone contained in ATCC Deposit Number 209343 209342; (m) a nucleotide sequence encoding the mature TR11 receptor having the amino acid sequences encoded by the cDNA clone contained in ATCC Deposit Number 209341; (n) a nucleotide sequence encoding the mature TR11SV1 receptor having the amino acid sequences encoded by the cDNA clone contained in ATCC Deposit Number 209342 209343; (o) a nucleotide sequence encoding the mature TR11SV2 receptor having the amino acid sequences encoded by the cDNA clone contained in ATCC Deposit Number 209343 209342; (p) a nucleotide sequence encoding the TR11 receptor extracellular domain; (q) a nucleotide sequence encoding the TR11SV1 receptor extracellular domain; (r) a nucleotide sequence encoding the TR11SV2 receptor extracellular domain; (s) a nucleotide sequence encoding the TR11 receptor transmembrane domain; (t) a nucleotide sequence encoding the TR11SV1 receptor transmembrane domain; (u) a nucleotide sequence encoding the TR11SV2 receptor transmembrane domain; (v) a nucleotide sequence encoding the TR11 receptor intracellular domain; (w) a nucleotide sequence encoding the TR11SV1 receptor intracellular domain; (x) a nucleotide sequence encoding the TR11SV2 receptor intracellular domain; (y) a nucleotide sequence encoding the TR11 receptor extracellular and intracellular domains with all or part of the transmembrane domain deleted; (z) a nucleotide sequence encoding the TR11SV1 receptor extracellular and intracellular domains with all or part of the transmembrane domain deleted; (aa) a nucleotide sequence encoding the TR11SV2 receptor extracellular and intracellular domains with all or part of the transmembrane domain deleted; and (bb) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), (x), (y), (z) or (aa). Polypeptides encoded by these polynucleotides are also encompassed by the invention.

The paragraph spanning lines 1-36 of page 40 has been replaced with the following amended paragraph:

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the TR11, TR11SV1 and/or TR11SV2 polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the TR11, TR11SV1 and/or TR11SV2 polypeptide sequences (e.g., those recited in SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6, or contained in the respective TR11, TR11SV1 and TR11SV2 polypeptides encoded by the respective clones HHEAC71, ~~HT5EA78 and HCFAZ22~~ HCFAZ22 and HT5EA78). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a TR11, TR11SV1 or TR11SV2 fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a TR11-Fc, TR11SV1-Fc or TR11SV2-Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, oseteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more TR11, TR11SV1, TR11SV2 polypeptides of the invention are joined through synthetic linkers (e.g., peptide,

carbohydrate or soluble polymer linkers). Examples include, but are not limited to, those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple TR11, TR11SV1, TR11SV2 polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.

The paragraph spanning lines 3-18 of page 76 has been replaced with the following amended paragraph:

Preferably, the polynucleotides of the invention (including TR11, TR11SV1 and/or TR11SV2 fragments, variants, derivatives and analogs) encode a polypeptide which demonstrates a TR11, TR11SV1 and/or TR11SV2 functional activity. By a polypeptide demonstrating "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length and/or secreted TR11, TR11SV1 and/or TR11SV2 polypeptide. Such functional activities include, but are not limited to, biological activity (e.g., ability to regulate (i.e., stimulate or inhibit) B cell proliferation (e.g., see Example 31), differentiation, activation, and/or survival), antigenicity [ability to bind (or compete with a TR11, TR11SV1 and/or TR11SV2 polypeptide for binding) to an anti-TR11 antibody, anti-TR11SV1 antibody and/or anti-TR11SV2 antibody], immunogenicity (ability to generate antibody which binds to a TR11, TR11SV1 and/or TR11SV2 polypeptide), ability to form multimers with TR11, TR11SV1 and/or TR11SV2 polypeptides of the invention, and ability to bind to a receptor or ligand for a TR11, TR11SV1 and/or TR11SV2 (e.g., Endokine-alpha (*See*, International Publication No. WO 98/07880 and Example 28 27)).

The paragraph spanning lines 1-9 of page 77 has been replaced with the following amended paragraph:

In another embodiment, where a TR11, TR11SV1 and/or TR11SV2 ligand is identified (e.g., Endokine-alpha (*See*, International Publication No. WO 98/07880 and Example 28 27)), or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky, E., et al., 1995, *Microbiol. Rev.* 59:94-123. In another embodiment, physiological correlates of

TR11, TR11SV1 and/or TR11SV2 binding to its substrates (signal transduction) can be assayed.

The paragraph spanning lines 25-37 of page 83 has been replaced with the following amended paragraph:

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:4, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 209342 209343 or encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NO:3 or contained in ATCC deposit No. 209342 209343 under stringent hybridization conditions or lower stringency hybridization conditions as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:3), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or lower stringency hybridization conditions defined *supra*.

The paragraph spanning lines 1-13 of page 84 has been replaced with the following amended paragraph:

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:6, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 209343 209342 or encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NO:5 or contained in ATCC deposit No. 209343 209342 under stringent hybridization conditions or lower stringency hybridization conditions as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:5), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand

under stringent hybridization conditions or lower stringency hybridization conditions defined *supra*.

The paragraph spanning lines 17-32 of page 136 has been replaced with the following amended paragraph:

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in TR11, TR11SV1 and/or TR11SV2, or the complementary strand thereof, and/or to nucleotide sequences contained in the deposited clones HHEAC71, ~~HT5EA78 and HCFAZ22~~ HCFAZ22 and HT5EA78, respectively. In one embodiment, antisense sequence is generated internally by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

In the claims:

Claims 47 and 48 drawn to non-elected inventions have been cancelled without prejudice.

Claims 19 and 33 have been replaced with the following amended claims:

19. (Amended) A method of inhibiting binding of Endokine-alpha to endogenous Endokine-alpha receptors in a mammal comprising administering to said mammal an effective amount of a TR11 polypeptide selected from the group consisting of:
- (a) a polypeptide whose amino acid sequence comprises amino acid residues -25-137 of SEQ ID NO:2;
 - (b) a polypeptide whose amino acid sequence comprises amino acid residues 1-137 of SEQ ID NO:2;
 - (c) a polypeptide whose amino acid sequence comprises amino acid residues 1-114 of SEQ ID NO:2; and
 - (d) ~~a polypeptide whose amino acid sequence comprises amino acid residues 25-139 of SEQ ID NO:2;~~
 - (e) ~~a polypeptide whose amino acid sequence comprises amino acid residues 21-139 of SEQ ID NO:2;~~
 - (f) ~~a polypeptide whose amino acid sequence comprises amino acid residues 8-129 of SEQ ID NO:2;~~
 - (g) ~~a polypeptide whose amino acid sequence comprises amino acid residues 8-48 of SEQ ID NO:2;~~
 - (h) ~~a polypeptide whose amino acid sequence comprises amino acid residues 49-88 of SEQ ID NO:2; and~~
 - (i) ~~a polypeptide whose amino acid sequence comprises amino acid residues 89-129 of SEQ ID NO:2;~~

(d) a polypeptide fragment of the polypeptide of SEQ ID NO:2, wherein said fragment binds endokine-alpha;

in a pharmaceutically acceptable carrier.

33. (Amended) A method of inhibiting binding of Endokine-alpha to endogenous Endokine-alpha receptors in a mammal comprising administering to said mammal an effective amount of a TR11 polypeptide selected from the group consisting of:

- (a) a polypeptide whose amino acid sequence comprises ~~amino-acid residues residues -25-137 the signal sequence and the extracellular domain~~ of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209341;
- (b) a polypeptide whose amino acid sequence comprises ~~amino-acid residues residues -1-137 the extracellular domain~~ of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209341; and
- (c) ~~a polypeptide whose amino acid sequence comprises amino-acid residues -1-114 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209341;~~
- (d) ~~a polypeptide whose amino acid sequence comprises amino-acid residues -25-139 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209341;~~
- (e) ~~a polypeptide whose amino acid sequence comprises amino-acid residues -21-139 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209341;~~
- (f) ~~a polypeptide whose amino acid sequence comprises amino-acid residues -8-129 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209341;~~

(g) — a polypeptide whose amino acid sequence comprises amino acid residues 8-48 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209341;

(h) — a polypeptide whose amino acid sequence comprises amino acid residues 49-88 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209341; and

(i) — a polypeptide whose amino acid sequence comprises amino acid residues 89-129 of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209341;

(c) a polypeptide fragment of the polypeptide encoded by the cDNA contained in ATCC Deposit Number 209341; wherein said fragment binds endokine-alpha;

in a pharmaceutically acceptable carrier.